TUBERCULOSIS: A RESURGENT DISEASE IN IMMUNOSUPPRESSED PATIENTS

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Abstract. A total of 136 patients, 67 HIV, 69 diabetes mellitus (DM) with or without (±) end-stage renal disease (ESRD), were registered for tuberculosis treatment at the National Tuberculosis Center (NTBC) from May to December, 2003. Ages ranged from 21-78 years (median 57.7 years) in TB/DM patients, and 21-62 (mean 37.6 ± 8.3 years) in TB/HIV patients. TB was significantly found in younger and single HIV patients, but in older and married DM patients ($p<0.05$). Male patients in both groups were strongly associated with TB, while females more commonly had TB with DM ($p<0.05$). The majority of these patients were Malays, unemployed, and resided in Kuala Lumpur territory; however, no statistically significant difference was found between the 2 groups. Smoking, IVDUs and hepatitis C virus (HCV) infection were more significantly found in TB/HIV patients and further analysis showed that pulmonary TB was strongly associated with HCV infection in these patients ($p<0.05$). Pulmonary TB (62; 89.9%) was the most common type found in both groups and was a markedly more common disease location in TB/DM patients, while extrapulmonary TB (21; 31.3%) and miliary TB (14; 21%) were significantly higher in TB/HIV patients. Cough with or without sputum, fever and loss of appetite and/or weight were common clinical presentations in both groups. Nevertheless, fever (54; 80.6%) and lymphadenopathy (17; 25.4%) were significantly related to TB/HIV patients ($p<0.05$). Interestingly, the presence of BCG vaccination and positive tuberculin skin test were stronger in TB/HIV (27; 40.3%) and TB/DM (20; 29%) patients, respectively ($p<0.05$). Overall, regular 6-, 9- and 12-months' anti-tubercular therapy (ATT) were routine practice, and EHRZ+B6 was the most common regimen used. The highest percentage of patients with treatment success were in both groups with 6 months' ATT; however, a significantly higher percentage was found in TB/DM (24; 34.8%) than TB/HIV (13; 19.4%) ($p<0.05$). A success rate of 15 (21.7%) was noted for TB/DM patients with 9 months' ATT, which was similar to both groups with the 12-month regimen. A higher percentage failure rate (lost to follow-up) was seen in TB/HIV (19; 28.4%) patients. Nine patients were reported to have anti-tubercular-drug side-effects, such as drug-induced hepatitis, blurred vision, and skin rash. No cases of drug resistance or death were notified among these patients.

INTRODUCTION

Tuberculosis (TB) is one of the most devastating diseases, primarily due to several decades of neglect, and presents a global health threat of escalating proportions; in addition, TB is the second leading infectious cause of mortality today after HIV/AIDS (Nayyar and Jain, 2005). TB continues to be a major public health problem, not only in developed countries, but also in almost all developing countries (Siriram and Arvind, 1992; Al Shohaib, 2000). Sub-Saharan Africa carries the overwhelming share of the global burden of HIV/AIDS and of HIV-associated TB (Maher *et al*, 2005). In a given population, one expects to see TB, DM and HIV in varying combinations. TB may lack the characteristic clinical and histological picture due to associated depressed cell-mediated immunity in both DM and HIV, and TB may have an unusual clinical presentation and cytology picture (Sridhar *et al*, 2002). Moreover, HIV not only makes the diagnosis of TB more difficult; it also contributes to an increase in TB incidence (Narain *et al*, 1992; Raviglione *et al*, 1992). This study was therefore conducted to determine the comparative distributions of tuberculosis in terms of epidemiological, clinical manifestations, investigation and treatment outcomes, between diabetic and/or end-stage renal failure (ESRD) and HIV-infected patients. These findings contribute significant evidence for better understanding and proper management, including recommendations on the course of tuberculosis in these immunosuppressed patients.

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MATERIALS AND METHODS

Patients

A total of 136 patients, 67 HIV, 61 diabetes mellitus (DM), and 8 end-stage renal disease (ESRD), were

registered for tuberculosis treatment at the National Tuberculosis Center (NTBC) from May to December, 2003. This center is a tertiary-level national reference center for respiratory diseases in Kuala Lumpur, Malaysia. Any person with a respiratory problem can attend this center without a physician's referral. The majority of notified TB cases in Kuala Lumpur territory each year are treated there. Data from each patient's medical record were reviewed retrospectively. Socio-demographic profiles, clinical presentations, investigation results, treatment, patient compliance with therapy, and outcomes of therapy response, were included in a standardized data collection sheet. AIDS-defining illnesses were also based on the 1993 CDC classification.

The case definitions were obtained from the World Health Organization (WHO, 2002).

A case of tuberculosis was defined as a patient in whom tuberculosis has been bacteriologically confirmed, or has been diagnosed by a clinician.

A pulmonary tuberculosis, sputum-smear-positive (PTB+) case was defined as two or more initial sputum smear examinations positive for acid-fast bacilli (AFB) or one sputum smear examination positive for AFB plus radiological abnormalities consistent with active pulmonary tuberculosis as determined by a clinician, or one sputum smear positive for AFB plus sputum culture positive for *M. tuberculosis*.

A pulmonary tuberculosis, sputum-smear-negative (PTB-) case was defined as a case of pulmonary tuberculosis not meeting the above definition for smear-positive TB. In keeping with good clinical and public health practices, diagnostic criteria should include: at least three sputum specimens negative for AFB, and radiographic abnormalities consistent with active pulmonary tuberculosis, and no response to a course of broad-spectrum antibiotics, and decision by a clinician to treat with a full course of anti-tuberculosis chemotherapy.

An extrapulmonary tuberculosis case was defined as tuberculosis of organs other than the lungs, such as pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones, and meninges. Disease should be based on one culture-positive specimen, or histological or strong clinical evidence consistent with active extrapulmonary tuberculosis, followed by a decision by a clinician to treat with a full course of anti-tuberculosis chemotherapy.

Categories of patients for registration

New: a patient who has never had treatment for TB or has taken anti-tuberculosis drugs for less than one month.

Relapse: a patient previously treated for TB who has been declared cured or has completed treatment, and is diagnosed with bacteriologically positive (smear or culture) tuberculosis.

Failure: a patient who, while on treatment, is sputum-smear-positive at 5 months or later during the course of treatment.

Return after default: a patient who returns for treatment with positive bacteriology, following an interruption of treatment for two or more months.

Transfer in: A patient who has been transferred from another tuberculosis register to continue treatment.

Categories of treatment outcomes

Cure: a patient who is sputum-smear-negative in the last month of treatment and on at least one previous occasion.

Treatment completed: a patient who has completed treatment but who does not meet the criteria to be classified as cured or failure.

Treatment failure: a patient who is sputum-smear-positive at five months or later during treatment.

Died: a patient who dies for any reason during the course of treatment.

Defaulter: a patient whose treatment was interrupted for 2 or more consecutive months.

Transfer out: a patient who has been transferred to another unit and for whom the treatment outcome is not known.

Treatment success: a patient who is cured and who has completed treatment.

Statistical analysis

The data were analyzed using the statistical software, SPSS version 10 (SPSS Inc, Chicago, Ill, USA). Data with quantitative variables were expressed by mean (± SD) and range, while qualitative variables were estimated by frequency and percentage. Statistical analysis was estimated using chi-square test, where appropriate. A p-value of <0.05 was regarded as statistically significant.

RESULTS

Table 1 shows the comparative distribution of demographic profiles between 69 TB/DM and/or end-stage renal disease (ESRD) and 67 TB/HIV patients. Ages ranged from 21 to 78 (median 57.7)

Table 1
Demographic characteristics of 136 immunosppressed patients attended at the National Tuberculosis Center (NTBC).

Variables	No. of TB patients (%)		p-value
	TB/DM ± ESRD[a] (69)	TB/ HIV (67)	
Range of age	21-78 years Median = 57.7	21-62 years Mean ± SD = 37.6 ± 8.32	
Age group (year)			0.000
15-24	2 (2.9)	5 (7.5)	
25-34	0	15 (22.4)	
35-44	3 (4.3)	36 (53.7)	
45-54	18 (26)	10 (15)	
≥ 55	46 (68.7)	1 (1.5)	
Sex			0.000
Male	42 (60.1)	59 (88)	
Female	27 (39.1)	8 (12)	
Race			0.534
Malay	36 (52.1)	39 (58.2)	
Chinese	18 (26)	13 (19.4)	
Indian	11 (16)	8 (12)	
Foreigner	4 (5.8)	7 (10.5)	
Marital status			0.000
Single	6 (8.7)	42 (62.7)	
Married	63 (91.3)	25 (37.3)	
Career			0.229
Unemployed	56 (81.2)	46 (68.7)	
Laborer	7 (10.2)	10 (15)	
Nonlaborer	6 (8.7)	11 (16.4)	
Address			0.973
Kuala Lumpur	41 (59.4)	40 (59.7)	
Outsider	28 (40.6)	27 (40.3)	
Mode of HIV transmission			0.000
Heterosexual	0	8 (12)	
Intravenous drug users (IVDU)	0	42 (62.7)	
Heterosexual-IVDU	0	2 (3)	
No record	69 (100)	15 (22.4)	
Other risk factors			0.000
Smoking	19 (27.5)	28 (41.8)	
Alcohol consumption	0	8 (12)	
Smoking and drinking	3 (4.3)	7 (10.5)	
No record	47 (68.1)	24 (35.8)	
HBV infection			0.001
Negative	16 (23.2)	31 (46.3)	
Positive	1 (1.5)	6 (9)	
No record	52 (75.4)	30 (44.8)	
HCV infection			0.000
Negative	13 (18.8)	7 (10.5)	
Positive	2 (2.9)	31 (46.3)	
No record	54 (78.3)	29 (43.3)	

(Continued)

Table 1
(Continued)

Variables	No. of TB patients (%)		p-value
	TB/DM ± ESRD[a] (69)	TB/ HIV (67)	
BCG vaccination			0.001
No	19 (27.5)	3 (4.5)	
Yes	19 (27.5)	27 (40.3)	
No record	31 (45)	37 (55.2)	
History of contact previous TB			0.954
No	62 (89.9)	60 (89.5)	
Yes	7 (10.1)	7 (10.5)	
Case category			
New case	67 (97.1)	61 (91)	0.354
History of previous tuberculosis			
With completed treatment (relapse)	1 (1.5)	3 (4.5)	
With defaulted treatment	0	2 (3.0)	
No treatment record	1 (1.5)	1 (1.5)	
Type of tuberculosis			0.001
Pulmonary TB	60 (87)	39 (58.2)	
Pulmonary TB-extrapulmonary TB	2 (2.9)	6 (9)	
Extrapulmonary TB	7 (10.1)	21 (31.3)	

[a]TB/DM ± ESRD means TB/DM with or without ESRD.

years in TB/DM patients, and 21-62 (mean 37.6 ± 8.3) years in TB/HIV patients. TB was more significant in the younger and single HIV cases, but in older and married DM patients. Male patients in both groups were strongly associated with TB; while females more commonly had TB with DM. The majority of these patients were Malay, unemployed, and resided in Kuala Lumpur territory; however, no statistically significant difference was found between the 2 groups. Smoking, IVDU, hepatitis B virus (HBV), hepatitis C virus (HCV) infections, and BCG vaccination, were more significantly found in TB/HIV patients. Further analysis showed that pulmonary TB was strongly associated with HCV infection in HIV patients. Newly diagnosed TB cases were found in TB/DM (67; 97%) and TB/HIV (61; 91%) patients. From our data, 8 patients had a history of previous TB–4 (3 HIV and 1 DM) cases of relapse, 2 cases of HIV with default to treatment, and the remaining 2 (1 HIV and 1 DM) cases were unrecorded. The lung was the most common location for DM (60; 87%) and HIV (39; 58.2%) patients. Each case of TB lung and kidney or pleura was diagnosed in DM patients, whilst 6 cases of TB lung and lymph node and 1 case of TB lung, lymph node and pleura were diagnosed in HIV-positive patients. Miliary was the most frequent site of extrapulmonary TB (ETB); which was found in 8 HIV patients and 6 cases of miliary and disseminated (lymph node, pleura, hip and mandibular) were also reported in these patients. The lymph node was the most common ETB found in DM patients, while each case of miliary, spine, skin and eye were also diagnosed in these patients. Overall, PTB was more significantly diagnosed in TB/DM patients, and ETB was more frequently notified in TB/HIV patients.

This study showed that cough with or without sputum, fever and loss of appetite and/or weight were more common clinical presentations in both groups. Nevertheless, fever and lymphadenopathy were more significantly found in TB/HIV patients. Surprisingly, positive tuberculin skin test was strongly related to TB/DM patients. Sputum smear (32; 46.4% in TB/DM *vs* 27; 40.3% in TB/HIV) and culture (37; 53.6% in TB/DM *vs* 29; 43.3% in TB/HIV) were used to verify the presence of *Mycobacterium* TB; however, there was no statistical significance. The chest radiograph was a very useful tool in this study; where the majority of HIV (29; 43.3%) and DM ± ESRD (37; 53.6%) patients showed typical upper lobe opacity among TB-positive patients. Overall, the regular 6-, 9- and 12-months' anti-tubercular therapy (ATT) were registered; while EHRZ+B6 was the most common regimen used in these patients. The highest percentage of patients with treatment success was found in both groups of 6-month anti-tubercular regimen; however, a significantly higher percentage was

found in TB/DM (24; 34.8%) than TB/HIV (13; 19.4%) patients. A success rate of 15 (21.7%) was also found in TB/DM patients with 9 months' ATT; which was similar to the 2 12-month-regimen groups. A higher percentage failure rate (lost to follow-up) was seen in TB/HIV (19; 28.4%). Nine patients were reported to have side-effects to anti-tubercular drugs, such as drug-induced hepatitis, blurred vision, and skin rash. No case of drug resistance or death was notified during the study, as demonstrated in Table 2.

Table 2
Clinical manifestations and treatment outcomes of these patients.

Variables	No. of patients		p-value
	TB/DM ± ESRD[a] (69)	TB/ HIV (67)	
Clinical manifestations			
Fever	35 (50.7)	54 (80.6)	0.000
Cough	57 (82.6)	56 (83.6)	0.880
Sputum	42 (60.9)	37 (55.2)	0.505
Hemoptysis	18 (26.1)	10 (15)	0.108
Loss of appetite and/or weight	48 (69.6)	55 (82)	0.088
Lymphadenopathy (cervical)	0	17 (25.4)	0.000
Dyspnea	12 (17.4)	15 (22.4)	0.465
Others *eg,* chest, back, or abdomen pain	9 (13)	6 (9)	0.639
Investigation			
Tuberculin skin test			0.002
Negative	15 (21.7)	16 (24)	
Positive	20 (29)	4 (6)	
No record	34 (49.3)	47 (70.2)	
Sputum smear			0.676
Negative	36 (52.2)	38 (56.7)	
Positive	32 (46.4)	27 (40.3)	
No record	1 (1.5)	2 (3)	
Sputum culture			0.340
Negative	27 (39)	29 (43.3)	
Positive	37 (53.6)	29 (43.3)	
No record	5 (7.3)	9 (13.4)	
Chest radiograph findings			0.000
Normal	6 (8.7)	4 (6)	
Positive for PTB	60 (87)	38 (56.7)	
Positive for PTB and disseminated	2 (2.9)	7 (10.5)	
Positive for ETB	2 (2.9)	17 (25.4)	
Tissue biopsy			0.415
Positive	7 (10.2)	5 (7.5)	
No record	3 (4.4)	0	
Other results			
CT scan, MRI, ultra-sound, echocardiogram, PCR, pleural fluid and ophthalmoscope	5 (7.3)	3 (4.5)	0.505
Treatment outcomes			
Loss to follow-up	15 (21.7)	19 (28.4)	0.373
Transfer out	2 (2.9)	15 (22.4)	0.001
Ongoing < 6 months	8 (11.6)	5 (7.5)	-
Success ≥ 6 months	24 (34.8)	13 (19.4)	0.044
Success ≥ 9 months	15 (21.7)	8 (12)	0.204
Success ≥ 12 months	5 (7.3)	6 (9)	0.715

[a]TB/DM ± ESRD means TB/DM with or without ESRD.

In addition, it is important to mention TB in 8 of the ESRD patients whom we were able to include during this study; 2 were diagnosed with DM as an underlying cause, and the other 6 patients showed no record. The majority of these patients were in the age group ≥45 years (5 patients) and female (6 patients). Only 1 patient showed positive for tuberculin skin test and 5 patients had BCG vaccination. Overall, patients had typical clinical pulmonary manifestation, *eg* fever (2 cases), cough (5), sputum (2), hemoptysis (1), and loss of weight and/or appetite (3). Chest radiograph was the main investigation to confirm all 6 patients with pulmonary TB. Five patients presented with pulmonary tuberculosis, 1 case with pulmonary and disseminated TB (lung and kidney), and 2 cases with ETB (1 each for miliary and skin). The most common anti-tubercular drug regimen used was HRZ+B6. The outcome showed that 3 patients had treatment success in durations of 6, 9, and 12 months, while 3 patients were treatment ongoing, and the remaining 2 were lost to follow-up. No case of death or drug resistance was notified in these patients during this study (data not shown).

DISCUSSION

The proportion of tuberculosis developing particularly from compromized hosts in high-risk groups is especially high (Anonymous, 2003). From our data, the trend of TB was significantly higher among males (Stead and To, 1987; Holmes *et al*, 1998; Pérez-Guzmán *et al*, 2003) in both groups, younger and single HIV (25-44 years) but in older and married DM (≥ 45 years) patients. This finding has been reported elsewhere and coincides with the existing epidemiological viewpoint. Smoking was shown in a high percentage of both groups, but more significantly higher in TB/HIV patients. One study interestingly reported that persons with exposure to active and passive smoking had a higher risk of pulmonary TB; therefore, an effective anti-smoking campaign is expected to have positive repercussions on TB incidence (Ariyothai *et al*, 2004). In addition, intravenous drug use and HCV infection were also found in markedly higher percentages among TB/HIV patients. Our finding conforms the strong associations of these important risk factors. Further studies are needed to assess the impact of the high prevalence of HCV co-infection on treatment outcomes, including tolerability and risk of anti-tuberculosis drug induced hepatotoxicity (Richards *et al*, 2006). The presence of BCG vaccination was even more commonly found in TB/HIV patients, and its role in TB prevention has been widely debated and questioned for its efficacy (Anonymous, 1990; Hashimoto, 1997; Lugosi, 1998; Mori, 2001). Nevertheless, we still support and recommend this primary TB preventive measure, since no alternative vaccine has currently been proven more effective in combating TB infection. We found few relapse cases; however, it plays no significant role in contributing to the occurrence of TB. One study showed that many other factors have contributed to relapse, such as delay in negative conversion of sputum culture, noncompliance, diabetes mellitus, and male cases aged in their 50s (Sasaki *et al*, 2003).

In the clinical scenario, pulmonary tuberculosis (PTB) is the most common form of TB, as reported in the literature and in our present study. PTB was higher in TB/DM patients; therefore, good control of DM is important to prevent the exacerbation of TB in these patients (Yoshitomi *et al*, 1998). Miliary TB was the most common ETB found in these patients, and had a higher rate in TB/HIV patients. The CXR finding is the most useful tool in diagnosing this form of TB, as evidenced in all cases of this study, to ensure early diagnosis and treatment to reduce the mortality rate in these patients. The majority of TB/DM patients showed opacity in the upper or middle zones of the lung. This finding is contrary to one recent study where DM patients were more likely to present with atypical radiological images and present with lower lung field lesions or cavities. The possibility of TB should always be considered for prompt diagnosis and management (Shaikh *et al*, 2003). Patients lost to follow-up were found in both groups, but the rate was higher among TB/HIV patients. The main reason for ineffective chemotherapy was noncompliance, while various factors have been verified, particularly in DM patients, such as severity of the DM course and its complications, the spread of TB, and the resistance of MTB to preparations (Voloshyn *et al*, 1999). Even though there was no drug resistance in these patients, one study has shown that MDR-TB was marginally higher in HIV-positive patients than in the non-HIV-infected population (Swaminathan *et al*, 2005). At this moment, we support INH prophylaxis; which has proven effective for HIV-infected patients in many settings. However, chemoprophylaxis must be administered to the patient for a long period, for at least 6 months, which may challenge patient compliance; in addition, a 2-month course of rifampicin and pyrazinamide daily can be used instead of INH alone (Narain and Lo, 2004).

TB in ESRD patients has consistently gained attention as part and parcel of DM and other chronic-disease patients. There is an increased risk (6-9 to 52.5-fold) of TB in these patients compared with the general population (Hussein *et al*, 2003). Surprisingly,

no such study has been reported in Southeast Asia, including Malaysia. From our analysis, all patients presented with typical respiratory signs and symptoms which can assist in diagnosis. One study suggested that such patients in an endemic area, who present with FUO, should be carefully evaluated for TB, and TB test therapy should immediately be performed (Erkoc *et al*, 2004). Moreover, FUO, reverse serum albumin/ globulin ratio, and unexplained hyperglycemia in these patients suggested the possibility of TB (Fang *et al*, 2004). Only 3 patients had extrapulmonary TB in our finding; however, one study showed that extrapulmonary TB is common in ESRD patients, and lymph node involvement was the most common extrapulmonary presentation (Lund *et al*, 2000). Regular tuberculin skin test (TST) evaluation, in combination with a chest X-ray, is a useful tool to detect *M. tuberculosis* infection in these patients (Wauter *et al*, 2004). Overall, TB prophylaxis is recommended in patients with a positive TST and radiographs suggesting old TB (Hussein *et al*, 2003), and its side effects were not a major problem in this group of patients (Agarwal *et al*, 2004). Therefore, identification of such factors related to TB in ESRD patients would be highly interesting and deserving of further larger-scale study, to enhance proper diagnosis and management for these patients.

In conclusion, this study showed some insights into TB, which remains a major challenge and continues to be an enormous public health problem, particularly for people in developing countries. The implementation of TB intervention and network collaborations, particularly in HIV-infected patients, needs to be highlighted, to help and generate common feasibilities to improve life expectancy among these patients and curb the future incidence of TB.

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